REMARKS/ARGUMENTS

The Present Invention and the Pending Claims

The present invention provides a method for selectively increasing glutamate and/or aspartate release in a central nervous system (CNS) locus in a site-specific manner. Claims 1-6 currently are pending.

Summary of the Office Action

The Office Action rejects claims 1-6 under 35 U.S.C. § 103(a) as being obvious over Tice et al. (U.S. Patent 5,360,610) in view of Heya et al. (EP 0 256 726 B1). Reconsideration of this rejection is respectfully requested.

Discussion of the Obviousness Rejection

The Office contends that it would have been obvious to one of ordinary skill in the art to use microencapsulated TRH disclosed by Heya et al. in the method of implanting biodegradable microparticles disclosed by Tice et al. The obviousness rejection is respectfully traversed because the cited references (alone or in combination) do not disclose or reasonably suggest the present invention as recited in the pending claims.

The pending claims provide prolonged release of TRH *in situ* at a central nervous system locus over a period of time by placing at least one biodegradable, non-bursting, *non-spherical* microstructure into a central nervous system locus. Tice et al. discloses implantation of polymeric microspheres to deliver bioactive agents to the central nervous system. These microspheres can include microcapsules, nanocapsules, and nanospheres (column 3, lines 7 - 9), which are all characterized as *spherical* particles (column 3, lines 10 - 18).

Heya et al. discloses a method of producing microcapsules comprising TRH. Similar to the disclosure of Tice et al., the microcapsules produced by the method of Heya et al. are *spherical* (page 5, lines 37 - 42, and page 9, lines 30 - 33). As previously stated in the Reply to Office Action filed on January 29, 2007, the microcapsule of Heya et al. is produced in such a manner that *only* spherical microcapsules are produced. The description of microcapsule manufacture starting on page 3, line 54 through page 5, line 33, includes the use of an oil/water liquid emulsion system. Such a system produces only spherical microparticles

(Birnbaum, D.T.; Brannon-Peppas, L. Microparticle Drug Delivery Systems *Drug Delivery Systems in Cancer Therapy.* Brown, D.M., ed.; Totowa: Humana Press Inc., 2003, pg. 118, of record). Specifically, the oil/water emulsion manufacturing process described in Heya et al. inherently generates spherical microcapsules as a result of the thermodynamically-driven minimization of water caging at the oil-water interface. This process results in a structure that has a minimum three dimensional surface area to volume ratio, commonly known as a sphere. Accordingly, a non-spherical microstructure, as recited in pending claims 1-6, could not be made using the manufacturing processes described in Heya et al.

Thus, the combination of Tice et al. and Heya et al. does not recite all the elements of the present invention, as defined by the pending claims. Moreover, the instant application discloses that the microstructures of the present invention include any shape in which, during erosion, the surface area of the microstructure decreases at a rate less than that of a microsphere (see, e.g., page 6, lines 17 - 20). Spherical particles, as described by Tice et al., are ill-suited to provide sustained drug delivery to central nervous system loci because the microspheres tend to disperse in extracellular cerebrospinal fluid (CSF) and are subject to nonspecific uptake and delivery to more distant sites in the brain by CSF through the circumventricular organs, glia and neurons themselves (see, e.g., page 2, lines 7 – 12). In contrast, *non-spherical* microstructures, as required by the pending claims, can be made larger than microspheres, which avoids the possibility of dispersion and optimizes the rate of drug delivery to the *in situ* site (see, e.g., page 7, lines 8 - 15).

The criticality in the use of *non-spherical* microstructures is further demonstrated in the Rule 132 Declaration of Michael J. Kubek, submitted herewith. As described in the Declaration, unlike a spherical construct, a *non-spherical* construct with a length greater than its width, such as a cylinder, microdisk, or a rod, can maintain a one dimensional length of sufficient size throughout the entire degradation process, thereby preventing migration during construct degradation. While both spherical and non-spherical constructs degrade at a constant rate proportionate to their surface area, only the *non-spherical* construct can maintain a sufficiently large one dimensional length to prevent diffusion of the implant over the entire degradation of the construct, enabling the therapy provider to more closely control the location of drug delivery (see Rule 132 Declaration). Controlling the location of drug

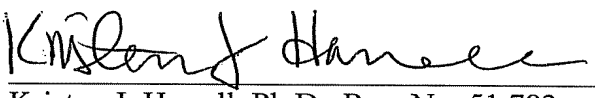
delivery provides prolonged release of TRH *in situ* to selectively increase glutamate and/or aspartate release in a CNS locus.

As neither Tice et al. nor Heya et al. disclose or suggest the use of non-spherical microstructures, and Applicant has addressed the criticality of using non-spherical microstructures, the present invention, as defined by the pending claims, cannot be considered obvious over the combination of the Tice and Heya references. In view of the foregoing, Applicant respectfully submits that the obviousness rejection is improper and should be withdrawn.

Conclusion

Applicant respectfully submits that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



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